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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,829	12/01/2003	Mee Len Chye	V9661.0043	7267

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,829	CHYE ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,4-11,14-19,22-27,30-33,36-39,42-49 and 51-58* is/are pending in the application.

4a) Of the above claim(s) *2,4-7 and 48* is/are withdrawn from consideration.

5)☒ Claim(s) *1,8-10,16-18,24-26,30-32,36-38,49,51,52 and 55-58* is/are allowed.

6)☒ Claim(s) *11,14,15,19,22,23,27,39,42-47,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. This application contains claims 2, 4-7 and 48 drawn to inventions nonelected with traverse in the response filed 9 December 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

3. The rejection of claims 1, 3 and 49-51 under 35 U.S.C. 102(a) as being anticipated by Xu et al (Plant Molecular Biology, 2001, 47:727-738) is withdrawn in light of the Declaration of Wen-Qing Qi, Xue-Zhi Ouyang, and Edward Yeung.

4. The rejection of claims 3, 50 and 55 under 35 U.S.C. 102(b) as being anticipated by Alcala et al (2001, GenBank Accession No. AW035333) is withdrawn in light of Applicant's amendment of the claims.

5. The rejection of claims 11, 14-15, 19, 22-23, 27, 33, 39 and 42 under 35 U.S.C. 102(b) as being anticipated by Johnson et al (1989, Proc. Natl. Acad. Sci. USA 86:9871-9875) taken with the evidence of Graham et al (1985, J. Biol. Chem. 260:6561-6564) is withdrawn in light of Applicant's amendment of the claims.

6. The rejection of claim 11, 19, 33 and 39 under 35 U.S.C. 102(b) as being anticipated by Anderson et al (29 February 2000, U.S. Patent 6,031,087) is withdrawn in light of Applicant's amendment of the claims.

7. The rejection of claims 1, 3, 8-9, 11-12, 14-17, 19-20, 30-31, 33-34, 36-37, 39-40, 42, 49-52 and 55-58 under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (PNAS, 86:9871-

9875, 1989) in view of Xu et al (2001, Plant Mol. Biol., 47:727-738) is withdrawn in light of the Declaration of Wen-Qing Qi, Xue-Zhi Ouyang, and Edward Yeung.

8. The rejection of claims 1, 3, 8, 10-11, 13, 16, 18, 19, 21, 30, 32-33, 35-36, 38-39, 41, 49-52, 55 and 56 under 35 U.S.C. 103(a) as being unpatentable over Xu et al (2001, Plant Mol. Biol., 47:727-738) in view of Daniell et al (U.S. Patent Application Publication No: 2004/0210966; effective filing date February 2001) and further in view of Zhang et al (Plant Physiology, 127:131-141, 2001, abstract) is withdrawn in light of the Declaration of Wen-Qing Qi, Xue-Zhi Ouyang, and Edward Yeung.

9. The rejection of claims 1, 3, 16, 17, 19, 20, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Solomon et al (1999, Plant Cell, 1 1:431-443) in view of Xu et al (2001, Plant Mol. Biol., 47:727-738) is withdrawn in light of the Declaration of Wen-Qing Qi, Xue-Zhi Ouyang, and Edward Yeung.

10. The rejection of claims 1, 3, 24, 25, 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Urwin et al (1998, Planta, 204: 472-479) in view of Xu et al (2001, Plant Mol. Biol., 47:727-738) is withdrawn in light of the Declaration of Wen-Qing Qi, Xue-Zhi Ouyang and Edward Yeung.

Claim Rejections - 35 USC § 112

11. Claims 46-47 and 53-54 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims are drawn to plasmids pSa7 or pMLVHisP or plants comprising them, which are subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 September 2005. Applicant's arguments filed 14 December 2005 have been fully considered but they are not persuasive.

Applicant urges that pSa7 and pMLVHisA were deposited under the terms of the Budapest Treaty (response pg 16-17).

This is not found persuasive because there is no an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent.

12. Claims 11, 14-15, 19, 22-23, 27, 33, 39, 42-46-47 and 53-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 September 2005, as applied to claims 3, 11-15, 19-23, 27-29, 33-35, 39-45, 50-52, and 55-58. Applicant's arguments filed 14 December 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to an isolated nucleic acid molecule having a nucleotide sequence that hybridizes to SEQ ID NO:1, wherein the nucleotide sequence encodes a protein having proteinase inhibitor activity.

Applicant does not describe an isolated nucleic acid molecule having a nucleotide sequence that hybridizes to SEQ ID NO:1, wherein the nucleotide sequence encodes a protein

having proteinase inhibitor activity. Applicant has not described any structural features of SEQ ID NO:1 that are essential for function and Applicant has not described if nucleic acid molecule having a nucleotide sequence that hybridizes to SEQ ID NO:1 possesses the structural features that are essential for function. Furthermore, there is no functional description of an isolated nucleic acid molecule having a nucleotide sequence that hybridizes to SEQ ID NO:1. In addition, Applicant does not describe the sufficient structural elements of a representative number of nucleic acids that encode a proteinase inhibitor II.

Hence, Applicant has not, in fact, described an isolated nucleic acid molecule having a nucleotide sequence that hybridizes to SEQ ID NO:1 wherein the nucleotide sequence encodes a protein having proteinase inhibitor activity within the full scope of the claims, therefore the specification fails to provide an adequate written description of the claimed genus.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed nucleic acids, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that the structure of SEQ ID NO:1 is the important element of the claims (response pg 18).

This is not found persuasive because the claimed nucleic acids do not have the structure of SEQ ID NO:1.

Applicant urges that the claims are directed to a genus of nucleic acids that hybridize with SEQ ID NO:1 and have proteinase inhibitor II activity; hybridization techniques are well-known, citing Sambrook, Chapter 8 (response pg 18).

This is not found persuasive because Sambrook Chapter 8 is drawn to cDNA synthesis, not DNA hybridization, and how it relates to DNA structure.

Applicant urges that one of skill in the art would not expect substantial variation among the species encompassed by the claims because the highly stringent hybridization conditions would yield structurally similar DNAs, and that is how the instant DNAs were isolated (response pg 18).

This is not found persuasive because the genus of proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1 is very broad, and includes nucleic acids that hybridize to only a small portion of SEQ ID NO:1; thus, SEQ ID NO:1 is not sufficient to represent their sequences. The only species described in the specification are SEQ ID NO:1 and 3. These species do not describe the full scope of this very broad genus.

13. Claims 11, 14-15, 19, 22-23, 27, 33, 39 and 42-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2, vectors and plants comprising them, and methods of using them to inhibit programmed cell death, does not reasonably provide enablement for proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1, vectors and plants comprising them, and methods of using them to inhibit programmed cell death. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 September 2005, as applied to claims 3, 11-15, 19-23, 27-29, 33-35, 39-47 and 50-58. Applicant's arguments filed 14 December 2005 have been fully considered but they are not persuasive.

The claims are broadly drawn to proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1, vectors comprising them, methods of transforming plant plastids with them to inhibit programmed cell death, and plants, including lettuce, thereby produced.

The instant specification, however, only provides guidance for only provide guidance for cloning and DNA sequence analysis of the 5'-end of the Sapin2b cDNA (pg 36); expression patterns of Sapin2a and Sapin2b (pg 45); localization of Sapin2a and Sapin2b mRNA and proteins in flowers (pg 45-46); immunogold labeling of Sapin2a and Sapin2b in S. americanum ovule (pg 47), generation of transgenic of lettuce with Sapin2a cDNA (pg 40 and 47); Southern blot analysis of transgenic lettuce (pg 48); expression of Sapin2a mRNA in transgenic lettuce (pg 49); trypsin and chymotrypsin inhibitory activities and endogenous trypsin- and chymotrypsin-like activity assays (pg 42 and 50); preliminary insect feeding assay with primary transgenic lettuce plants (pg 43 and 51); plasmid construction for plastid transformation of tobacco (pg 43 and 52) and screening of the plastid-transformed tobacco for integration of Sapin2a cDNA (pg 44).

The instant specification fails to provide guidance for proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1 or for methods of transformation of lettuce plastids.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain proteinase-inhibitor activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Making substitutions in proteins is not a predictable art. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid

at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate proteinase-inhibitor-encoding nucleic acids that hybridize to SEQ ID NO:1. Making all possible single amino acid substitutions in an 148 amino acid long protein like that encoded by SEQ ID NO:1 would require making and analyzing 19^{148} nucleic acids; these proteins would have 99.3% identity to SEQ ID NO:2. Because nucleic acids that hybridize to SEQ ID NO:1 would encode proteins with many amino acid substitutions, many more than 19^{148} nucleic acids would need to be made and analyzed. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1 would require undue experimentation.

As the specification does not describe the transformation of any plant plastid with a proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1 other than SEQ ID NOs:1 and 3, undue trial and error experimentation would be required to screen through the

myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with inhibited cell death, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that a nucleic acid that hybridizes to SEQ ID NO:1 can be found by screening cDNA libraries, including from Solanaceous plants, by hybridization or PCR, citing Sambrook and Amersham (response pg 20).

This is not found persuasive because the specification must teach how make the claimed nucleic acids. The claims are not limited to nucleic acids isolated from plant species, but include man-made nucleic acid sequences. Thus, the specification must teach how to make these nucleic acids; it does not. Furthermore, the specification fails to teach transformation of lettuce plastids.

Claim Rejections - 35 USC § 103

14. Claims 11, 14-15, 19, 22-23, 27, 33, 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daniell (US Patent Application 20030041353, filed February 2000) in view of each of Johnson et al (1989, Proc. Natl. Acad. Sci. USA 86:9871-9875) and Graham et al (1985, J. Biol. Chem. 260:6561-6564).

The claims are drawn to methods of transforming plant plastids with proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1.

Daniell disclose a method of plastid transformation (¶124 and 127). Daniell do not disclose transforming plant plastids with proteinase-inhibitor encoding nucleic acids that hybridize to SEQ ID NO:1.

Johnson et al teach tobacco plants nuclearly transformed with vectors comprising a 35S promoter operatively linked to the TI-II nucleic acid and methods of producing the protein in and isolating from the plants (pg 9872, right column, paragraphs 2-3; Fig. 1-2). Tobacco would be a "leafy vegetable".

Graham et al teach the TI-II nucleic acid, which is a proteinase-inhibitor encoding nucleic acid that would hybridize to SEQ ID NO:1 because it has a 35 nucleotide long stretch of 100% identity (see search results). The DNA was in a vector, which was in a recombinant host cell (pg 6561, right column, paragraphs 6-7).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation taught by Daniell, to transform plastids with the nucleic acid described in Johnson et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Daniel to do so (¶108). This method would be one of inhibiting programmed cell death in the plant, and would inhibit an endogenous trypsin- or chymotrypsin-like proteinase activity in the plant

15. Claims 1, 8-10, 16-18, 24-26, 30-32, 36-38, 49, 51-52 and 55-58 are allowed, given the failure of the prior art to teach or suggest an isolated nucleic acid encoding SEQ ID NO:2.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne Kubelik, Ph.D.
February 27, 2006